

Human ehrlichiosis: clinical aspects and treatment

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Case presentation

- 63 y old female, admitted august 2000
- prev. history of hepatorenal polycystosis, mild renal insuff. and art. HT
- one month history of fever >38.5 , anorexia, malaise and fatigue; no new clinical abnormality apart from fever
- Hb 11.3 g/dl, leuco 3230/mm³ (13% band neutro), thrombo 96 000/mm³

Case presentation (cont.)

- Extensive workup for FUO unrevealing (cultures, chest and abdo. CT, echocard., brain and abdo MRI, leuko.scan and PET, auto. antibodies...)
- No evidence for active inf with CMV, EBV, hep B,C, HIV, Hanta, Parvo B19, Leptospira, B. burgdorf, B. henselae, Brucella, Coxiella, R. conori/mooseri...

Case presentation (cont.)

- Empiric therapy with ceftazidime, netilmicin, teicoplanin, clarithromycin: worsening of symptoms
- transient generalized nonpruritic rash
- 7 weeks into illness, transfer to our hosp.: severely ill, $>40^{\circ}\text{C}$, bedridden, ecchymoses. Hb 9.4 g/dl, thrombocytes $14\,000/\text{mm}^3$, ALT $>5\times$ ULN, LDH 1697 U/L, lab ev. of DIC
- Bone marrow: only dysplasia in all lineages

Case presentation (cont.)

- Doxycycline 100 mg bid: immediate defervescence, progressive amelioration and normalisation of lab. abnormalities
- Serology for HGE-agent: IgG 1/32, IgM 1/16, six weeks later IgG 1/128
- No sequelae, no other diagnosis at 18 m FU

HGE: clinical features

- Short incubation period: 7-10 days
- Peak incidence as tick activity:
may-july (nymph) and november (adult)
- >60% identified tick bite
- >85% history of potential tick exposure
 - » *JAMA 1996;275:199*
 - » *CID 2000;31:554*

Ixodes ricinus



HGE: clinical features

- Most infections probably subclinical
 - seroconversion rate 11% in 1 y in highly tick endemic area in Sweden
 - » *EJCMID 2001;20:176*
 - 19/361 military recruits seroconverted in 10 m period in SW Germany, none remembered illness
 - » *Infection 2001;29:271*

HGE: clinical features

- Ratio of clinical to subclinical infection not known, probably increases with age
- Commonly identified clinical manifestation: “aspecific febrile illness”

Table 1. Frequency of presenting signs and symptoms with lab-confirmed human granulocytic ehrlichiosis.

CID 2000;31:554

Sign or symptom	New York (<i>n</i> = 18)	Upper Midwest (<i>n</i> = 41)
Fever (>38.3°C)	94	100
Rigors	39	98
Malaise	NA	98
Headache	61	85
Nausea	NA	39
Anorexia	NA	37
Arthralgias	78	27
Cough	NA	29
Confusion	NA	17
Rash	11	2

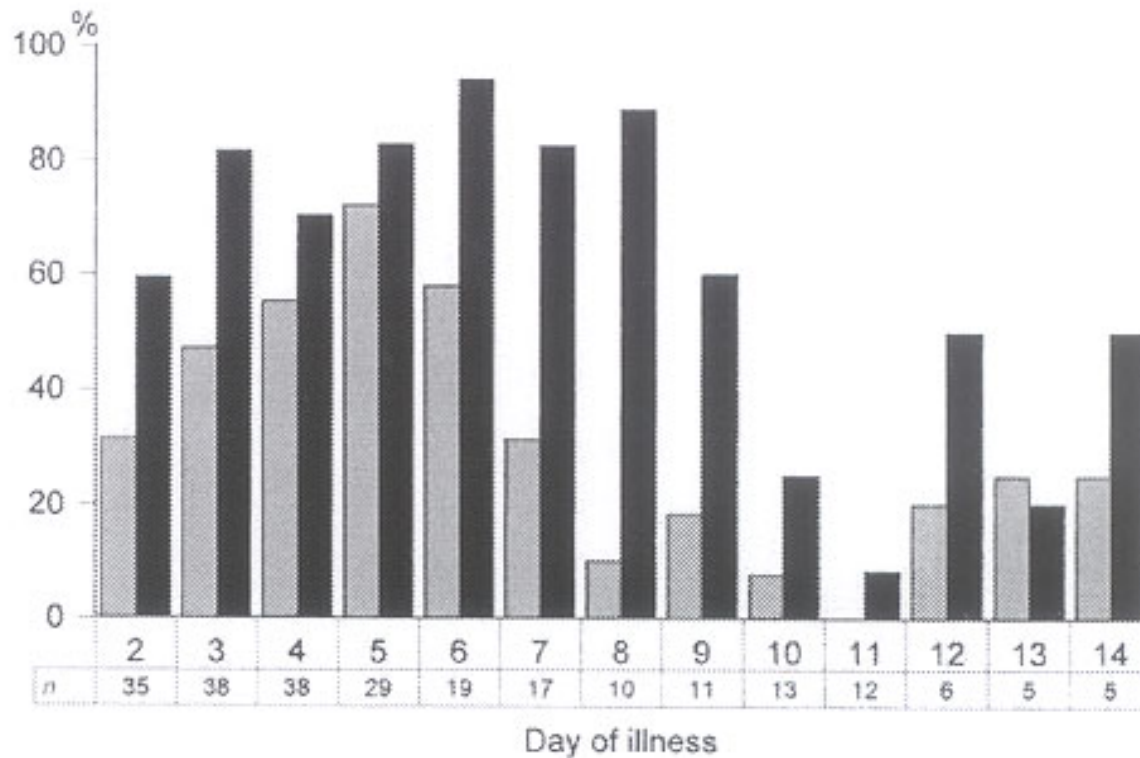
TABLE 181-2 Clinical and Laboratory Abnormalities in Human Monocytotropic and Granulocytotropic Ehrlichioses

Sign, Symptom, or Laboratory Finding	HME Patients with Abnormal Findings (%)	HGE Patients with Abnormal Findings (%)
Fever	97	94-100
Headache	81	61-85
Chills or rigors	67	39-98
Myalgia	68	78-98
Malaise	84	98
Nausea	48	39
Anorexia	66	37
Vomiting	37	34
Diarrhea	25	22
Abdominal pain	22	—
Rash	36	2-11
Cough	26	29
Dyspnea	23	—
Lymphadenopathy	25	—
Confusion	20	17
Leukopenia	60	50-59
Thrombocytopenia	68	59-92
Elevated AST	86	69-91
Elevated ALT	80	61
Elevated urea nitrogen	38	—
Elevated creatinine	29	70

Abbreviations: AST, Aspartate aminotransferase; ALT, alanine aminotransferase; HGE, human monocytotropic ehrlichiosis; HME, human monocytotropic ehrlichiosis.

Ehrlichiosis: lab features

CID 2001;32:862



Ehrlichiosis: lab features

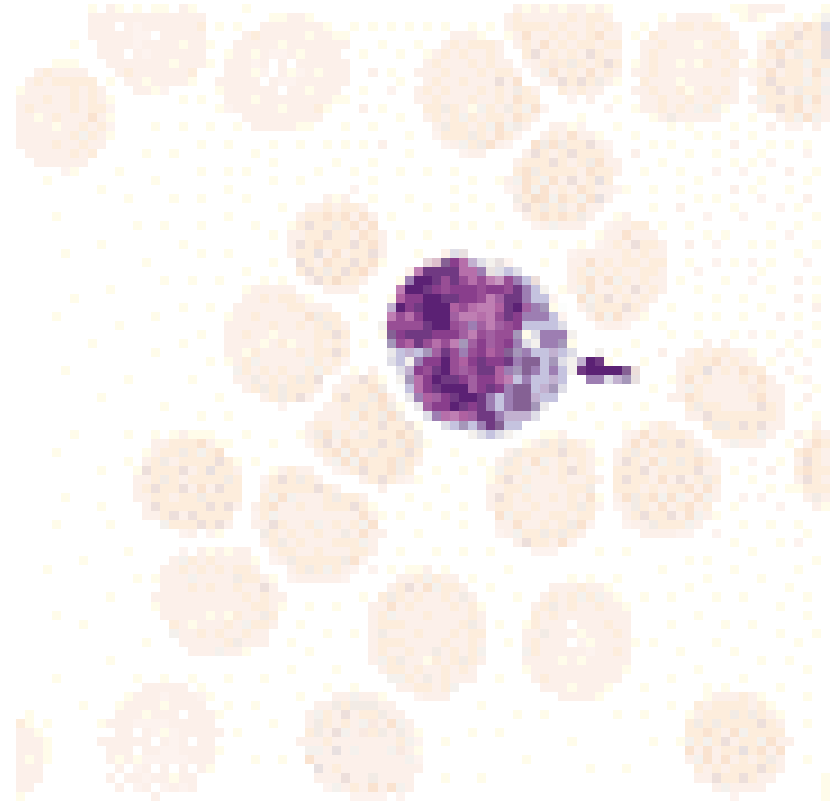
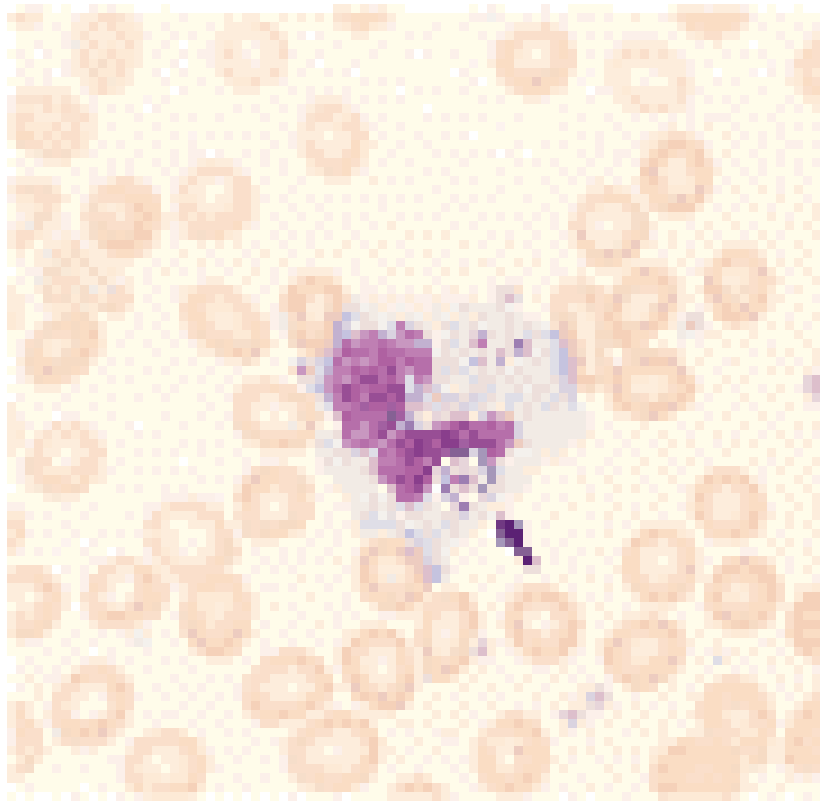
CID 2001;32:862

Table 2. Comparison of selected complete blood count parameters obtained from 111 patients who had documented human granulocytic ehrlichiosis (HGE) and 111 matched control patients who presented for evaluation of a nonspecific febrile illness that occurred after tick exposure in the upper Midwest.

Parameter	Value for		<i>P</i>
	Control patients	Patients with HGE	
Total WBC count, $\times 10^9$ cells/L	7.2 \pm 3.8	5.0 \pm 2.4	<.00001
Segmented neutrophils, $\times 10^9$ cells/L	4.8 \pm 3.3	3.1 \pm 2.0	<.0001
Segmented neutrophils, %	63.0 \pm 15.5	59.0 \pm 15.5	.057
Band neutrophils, $\times 10^9$ cells/L	0.42 \pm 0.44	0.83 \pm 0.65	<.00001
Band neutrophils, %	6.0 \pm 6.7	18.3 \pm 12.8	<.00001
Lymphocytes, $\times 10^9$ cells/L	1.4 \pm 1.1	0.95 \pm 0.92	.001
Lymphocytes, %	22.4 \pm 14.6	19.5 \pm 14.5	.14
Platelets, $\times 10^9$ cells/L	213 \pm 102	124 \pm 69	<.00001

NOTE. Data are \pm SD, unless otherwise indicated.

Morulae in mononuclear cells



Ehrlichiosis: complications

- Mortality
 - low but existing for HGE (<1%)
 - higher for HME (3%)
- Chronic infection not recorded in humans, protracted course rare

HGE: complications

- Shock, respiratory insufficiency, DIC, ARF
- rhabdomyolysis
- opportunistic infections
- cranial nerve involvement, plexopathy, GBS
- recurrent and prolonged disease in asplenic patients

Complications of HME, not (yet) recorded for HGE

- Meningoencefalitis
- cardiomyopathy
- nephrotic syndrome
- behaves as an opportunistic infection
 - hiv infection: mortality high (6/21!)
 - drug-induced immune suppression

Treatment of HGE: in vitro data

- No gold standard for determination of susceptibility
- No NCCLS breakpoints
- in vitro HL-60 cell culture:
 - MIC: >90% reduction at d 3
 - MBC: >90% reduction at d 8, after 5 d washout
 - » *AAC 2001; 45:786*

Treatment of HGE: in vitro data *AAC 2001; 45:786*

TABLE 1. Susceptibilities of six New York State isolates of *E. phagocytophila* to antimicrobials

Antibiotic	MIC ($\mu\text{g/ml}$)	MBC ($\mu\text{g/ml}$)
Doxycycline	≤ 0.125	0.125–0.5
Rifampin	≤ 0.125	≤ 0.125
Ofloxacin	≤ 2	≤ 2
Levofloxacin	≤ 1	≤ 1
Trovaflaxacin	≤ 0.032	≤ 0.032
Amoxicillin	≥ 32	≥ 32
Ceftriaxone	≥ 64	≥ 64
Chloramphenicol	> 16	$> 8^b$
Erythromycin ^a	> 8	> 8
Azithromycin	> 8	> 8
Clarithromycin	> 10	> 10
Amikacin	> 16	> 16

^a Erythromycin, erythromycin ethyl succinate.

^b For a single isolate, the MBC was $\leq 8 \mu\text{g/ml}$.

Treatment of HGE: in vitro data

- Based on in vitro data, doxycycline (and other tetrac.), rifampin and FQ good candidates
- *E. chaffeensis* not susceptible to FQ!

Treatment of ehrlichiosis

- doxycycline 100 mg bid for 7-14 d
 - no clinical trial to support use (but it works)
 - no trial investigated duration
- Case reports of successful treatment with rifampin (but spontaneous cure also occurs)
- Chloramfenicol failures reported: don't use

Prevention of ehrlichiosis

- Avoid tick exposure
- Remove tick <24 h: mouse data conflicting
 - no or very rare transmission of lab strain
 - » *JID 1998; 177:1422, JCM 1998; 36:3574*
 - infection with 2 out of 3 naturally infected ticks
 - » *JID 2001; 183 773*
- No data on AB after tick bite
- No vaccine

Ehrlichiosis

- Probably is around more than we think it is
- Sudden aspecific febrile illness with compatible lab and no obvious other cause: consider empiric doxy awaiting lab confirmation